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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,805	08/05/2003	Jean Rapin	10945.105003 (Neuro 102US	9760
20786	7590	10/15/2004	EXAMINER	
KING & SPALDING LLP 191 PEACHTREE STREET, N.E. ATLANTA, GA 30303-1763			CORDERO GARCIA, MARCELA M	
			ART UNIT	PAPER NUMBER
			1654	

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

10/635,805

**Applicant(s)**

RAPIN ET AL.

**Examiner**

Marcela M Cordero Garcia

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☒ Claim(s) 1-8 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/03 and 04/04</u> . | 6) <input type="checkbox"/> Other: ____.  |

## **DETAILED ACTION**

### ***Claim Objections***

Claims 1-8 are objected to because of the following informalities: In "A method for the treatment of treatment of postlesional diseases...", the words "treatment of" appear twice consecutively. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite because it is unclear as to whom or to what this effective amount is being administered. Therefore claim 1 currently reads on administering to any kind of subject, such as snails, bacteria, inanimate matter, etc. In addition, as drafted, claim 1 reads on administering to a subject in need thereof (therapeutic mode) and to a subject not in need thereof (prophylactic mode).

Claim 1 is rendered vague and indefinite by the phrase: "...R<sub>1</sub> is a residue from one of the aminoacids Phe, Tyr, Trp, Pro, which each may be optionally substituted with one or more (C<sub>1-5</sub>) alkoxy groups, (C<sub>1-5</sub>) alkyl groups or halogen atoms, as well as Ala, Val, Leu or Ile;". The claim is indefinite for the following reasons:

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a) It is not clear what the meaning of "optional substitution" is, e.g., does it mean replacing a hydrogen atom in the aromatic or proline rings for a different group, or does it mean modifying the amino acid residue in a different way, for example, replacing a hydrogen in the aliphatic portion of the residue or replacing an atom other than hydrogen?

b) It is not clear whether Ala, Val, Leu or Ile are to be optionally substituted within the amino acid residues Phe, Tyr, Trp and Pro, or if they are residues that can replace R<sub>1</sub> but that should not be optionally substituted.

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, second paragraph for the reasons set forth above.

With respect to the art rejections below, please note the following:

Alzheimer's disease, as referenced by Kan (Eur J Med Chem, 1992) is known in the art to be associated to brain lesions (amyloid  $\beta$ -protein plaques) whose composition is toxic (see, e.g., page 565, column 2 and page 566, column 1). Therefore, based upon the reference teachings, Alzheimer's disease can be classified as a postlesional disease of toxic origin.

In addition, please note that amnesia, as referenced by <http://www.smithsrisca.demon.co.uk/neuro-glossary.html> (accessed online, October 4, 2004), is known in the art to be associated, i.a., with bilateral lesions of either the hippocampal regions or the mammillary bodies, that may have originated by a

mechanical or physical agent (trauma) (<http://accessscience.com/>, search term 'trauma', accessed online, October 4, 2004), and therefore can be classified as a postlesional disease of traumatic origin.

Alzheimer's disease and amnesia are known in the art to be neurodegenerative disorders, as referenced by Henrichwark et al. (US 6080848). Ischemic heart disease may be caused, as is known in the art and referenced by Tedeshi et al. (US 6645518), by atherosclerotic lesions. Therefore ischemic heart disease can be classified as a postlesional disease of ischemic origin.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-4 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Masuyama et al. (US 6,410,685).

The instant claims are drawn to a method for the treatment of postlesional diseases of ischemic, traumatic or toxic origin, comprising administering an effective amount of a proline derivative of formula (I). Specific species for the method are, e.g., L-valyl-L-prolyl-L-proline and L-isoleucyl-L-prolyl-L-proline. Please note that the administered subject has not been defined and therefore the claims read upon the method with subjects not affected by any of the diseases.

Masuyama et al. teach the administration of valyl-L-prolyl-L-proline and L-isoleucyl-L-prolyl-L-proline to rats (examples 4-7).

Therefore, the reference is deemed to anticipate the instant claims above, as drafted.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshimasa et al. (JP 09169797)

Yoshimasa et al. teach biodegradable pharmaceutical compositions of a tripeptide encompassed by formula (I), e.g., Pro-Phe-Pro and Pro-Phe-Pro-NH<sub>2</sub> (see, e.g., abstract and example 3). These compositions inherently read upon a method of administration to a subject as it is indicated that the composition is decomposed in a living body and metabolized with no side effects (see, e.g., abstract).

Therefore, the reference is deemed to anticipate the instant claims above.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshimasa et al. (JP 09040577)

Yoshimasa et al. teach biodegradable pharmaceutical compositions of a tripeptide encompassed by formula (I), e.g., Pro-Phe-Pro and Pro-Phe-Pro-NH<sub>2</sub> (see, e.g. abstract and example 3). These compositions inherently read upon a method of administration to a subject as it is indicated that the composition is decomposed in vivo and metabolized with no side effects (see, e.g., abstract).

Therefore, the reference is deemed to anticipate the instant claims above.

Claims 1-6 are rejected under U.S.C. 102(b) as being anticipated by Hathaway et al. (WO 92/13549).

Hathaway et al. teach administration to rabbits of pharmaceutical compositions of peptides encompassed by formula (I), e.g., (see, e.g., abstract, pages 9-11 and 36-37).

Therefore, the reference is deemed to anticipate the instant claims above.

Claims 1, 3-7 are rejected under U.S.C. 102(b) as being anticipated by Maruyama et al. (EP 0445606 A1).

Maruyama et al. teach administration to rats of pharmaceutical compositions of peptides encompassed by formula (I) for (see e.g. page 2, lines 48-54).

Therefore, the reference is deemed to anticipate the instant claims above.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masuyama et al. (US 6,410,685).

Masuyama et al. beneficially teach the administration to a mouse of L-proline derivatives encompassing formula (I) (examples 4-7) and disclose that these compounds may be helpful against ischemic heart disease (see column 1, lines 32-36), which can be classified a postlesional disease of ischemic origin. Masuyama et al. teach the species L-valyl-L-prolyl-L-proline and L-isoleucyl-L-prolyl-L-proline (see, e.g., abstract).

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to have used the compounds and methods taught by Matsuyama in the prevention or treatment of postlesional diseases such as ischemic heart disease, since the compounds and their activity in regards to such diseases was known as beneficially taught by Masuyama et al. The adjustment of particular conventional working conditions therein (e.g., chemically modifying amino acid residues by alkylation or alkoxylation, determining a therapeutically effective amount to treat the specific diseases and/or the mode of administration) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.



From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshimasa et al. (JP 09169797).

Yoshimasa et al. teach the *in vivo* use of a pharmaceutical solution of, e.g. peptide Pro-Phe-Pro, which is encompassed by formula (I) (see, e.g., abstract). These compositions inherently read upon a method of administration to a subject as it is indicated that the composition is intended for *in vivo* use with no side effects (see, e.g., abstract).

Based upon the overall beneficial teachings provided by Yoshimasa et al. with respect to such peptide compositions, it would have been obvious at the time of the invention to adjust particular conventional working conditions therein (e.g., chemically modifying amino acid residues by alkylation or alkoxylation, replacing amino acid residues, as well as the actual administration of such compound to a subject in need thereof). This type of adjustment is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is *prima facie* obvious over the reference, especially in the absence of evidence to the contrary.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshimasa et al. (JP 09040577).

Yoshimasa et al. teach the in vivo use of a pharmaceutical solution of, e.g. peptide Pro-Phe-Pro, which is encompassed by formula (I) (see, e.g., abstract). These compositions inherently read upon a method of administration to a subject as it is indicated that the composition is decomposed in vivo and metabolized with no side effects (see, e.g., abstract).

Based upon the beneficial teachings provided by Yoshimasa et al., it would have been obvious at the time of the invention to have carried out the adjustment of particular conventional working conditions (e.g., chemically modifying amino acid residues by alkylation or alkoxylation, replacing amino acid residues, as well as the actual administration of such compound to a subject in need thereof) and this is therefore deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is prima facie obvious over the reference, especially in the absence of evidence to the contrary.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hathaway et al. (WO 92/13549)

Hathaway et al. teach administration to rabbits of pharmaceutical compositions of peptides encompassed by formula (I) for (see e.g. abstract, pages 9-11 and 36-37).

Yoshimasa et al. teach the in vivo use of a pharmaceutical solution of, e.g. peptide Pro-Phe-Pro, which is encompassed by formula (I) (see, e.g., abstract).

Based upon the overall beneficial teachings provided by Hathaway et al., it would have been obvious at the time of the invention to adjust particular conventional working conditions therein (e.g., amidating the proline, chemically modifying amino acid residues by alkylation or alkoxylation, replacing amino acid residues, as well as the actual administration of such compound to a subject in need thereof). This type of adjustment is therefore deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is prima facie obvious over the reference, especially in the absence of evidence to the contrary.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maruyama et al. (EP 0445606 A1).

Maruyama et al. teach administration to rats of pharmaceutical compositions of peptides encompassed by formula (I) for (see e.g. page 2, lines 48-54. Yoshimasa et al. teach the in vivo use of a pharmaceutical solution of, e.g. peptide Pro-Phe-Pro, which is encompassed by formula (I) (see, e.g., abstract).

Based upon the overall beneficial teachings provided by Maruyama et al., it would have been obvious at the time of the invention to adjust particular conventional working conditions therein (e.g., amidating the proline, chemically modifying amino acid residues by alkylation or alkoxylation, replacing amino acid residues, as well as the

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actual administration of such compound to a subject in need thereof). This type of adjustment is therefore deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

Thus, the invention as a whole is *prima facie* obvious over the reference, especially in the absence of evidence to the contrary.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 16 of copending Application No. 10/635,797.

The instantly claimed invention and the invention claimed in Application '797 are both drawn to a method of treating or preventing neurodegenerative diseases and/or postlesional diseases (such as Alzheimer's disease, in both cases) comprising administering an effective amount of a proline derivative of formula (I), e.g.,

Val-Pro-Pro or Ile-Pro-Pro. Further, the instantly claimed method encompasses and/or is encompassed by the claimed method of Application '797.

This is a provisional obviousness-type double patenting rejection.

### ***Information Disclosure Statement***

The information disclosure statements (IDSs) submitted on 11/03 and 04/04 were filed after the mailing date of the application on 08/05/2003. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

### ***Conclusion***

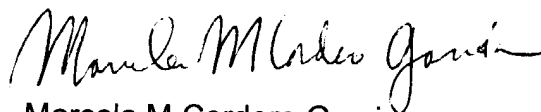
No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campbell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Marcela M Cordero Garcia  
Patent Examiner  
Art Unit 1654

MMCG 10-2004



CHRISTOPHER R. TATE  
PRIMARY EXAMINER